NTP
National Toxicology Program

The National Toxicology Program Update

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NTP Board of Scientific Counselors

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Outline

- Staff changes
- Meetings of note
  - Report on Carcinogens expert panel meetings
  - Technical Report Review Subcommittee meeting
- Selected program initiatives/updates
  - Evaluation criteria for non-cancer studies
  - Public health context for NTP study results
  - ICCVAM/NICEATM
  - Bisphenol A

Staff Changes

- Welcome
  - Dr. Michael DeVito
  - Dr. Scott Auerbach
  - Dr. Chad Blystone
  - Dr. Matt Stout
  - Ms. Kyla Taylor
- Active searches
  - CERHR (3)
  - NICEATM (1)
  - Pathology (2)
  - Program Operations Branch (1)
  - Toxicology Branch (2)
  - Office of Liaison, Policy and Review (1)
- Multiple IRTAs (postdocs)

Farewell

Dr. Ron Melnick

Dr. Doug Bristol

Meetings

- Report on Carcinogens
  - Expert panel for glass wool - May 9-10, 2009
  - Expert panel for formaldehyde - November 2-4, 2009
- Technical Reports Review Subcommittee - November 18-19, 2009
  - AIDS therapeutics (transplacental and GMM studies)
  - Bis(2-chloroethoxy)methane
  - 1-Bromopropane
  - Diethylamine
  - Ginseng
  - Milk thistle extract
  - Pulegone

Evaluation Criteria for NTP Studies

- Established level of evidence criteria for carcinogenicity
- New level of evidence criteria for non-cancer endpoints
  - Reproductive, developmental, and immunotoxicology studies
    - Pathology workshops
    - Board of Scientific Counselors Criteria Groups
      - Academia, government regulatory, industry
    - Working Group reports accepted by BSC - 20, 2008
    - Criteria revised - January 2009
    - Society of Toxicology Meeting unveiling criteria - March 15-19, 2009
    - First application: resveratrol immunotoxicity studies - Winter 2009
    - Drs. Paul Foster and Dori Germolec

- "Under the conditions of this study…"

NTP Roadmap for the 21st Century

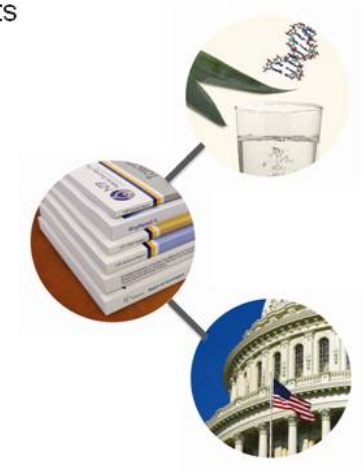
The NTP envisions that over the next decade utilization of our rapidly expanding knowledge of the physiological, biochemical, and molecular bases of disease will lead to the development of, and a gradual transition to, vastly improved and higher-throughput methods for predicting the toxicological impacts of environmental agents.

The NTP recognizes that this transition in methods from predominantly mammalian screens toward more in vitro systems and non-mammalian models must be carefully planned and systematically evaluated to assure scientific and regulatory utility.

The NTP is confident that through sustained leadership in creating and applying these mechanistic toxicology tools, we will generate the scientific information and understanding necessary for public health decision-makers to use these new tools to reduce the burden of environmental disease.

Responsibility for Scientific and Public Health Context

- Problem
  - High content data, HTS, genomics, Toxicology in the 21st century
  - Criteria for cancer and non-cancer endpoints
  - Societal expectations
- Solution
  - Internal discussions
  - Board of Scientific Counselors discussions
  - Executive Committee deliberations
- Expected outcome
  - Changes in organizational structure
  - Changes in programmatic expectations



NICEATM and ICCVAM

- Federal agencies adopted/endorsed 9 alternative test methods in 2008-09
  - Cytotoxicity test methods for estimating acute systemic toxicity (2)
  - *In vitro* ocular safety testing methods (2); International adoption by OECD
  - *In vitro* pyrogen test methods using human cells and cell-lines (5)
- NICEATM-ICCVAM Five-Year Plan (2008-2012)
  - Implementation plan developed and published
  - Interagency Research and Development Working Group established
- 2009 International peer review panel meetings
  - Allergic contact dermatitis: 3 non-radioactive methods; expanded applications
  - Ocular safety testing: modernized *in vivo* protocol (analgesics, anesthetics, and humane endpoints); 6 *in vitro* methods and testing strategies
- International validation study: ER transcriptional activation assay

NICEATM = NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
ICCVAM = Interagency Coordinating Committee on the Validation of Alternative Methods

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International Cooperation on Alternative Test Methods

- Memorandum of Cooperation
  - Signed at NIH - April 27, 2009
- Signatories
  - Dr. Linda Birnbaum, Director, NIEHS and NTP, USA
  - Dr. Masahiro Nishijima, Director, National Institute of Health Sciences, Japan
  - Dr. Elke Anklam, Director, Institute of Health, and Consumer Protection Joint Research Centre, European Commission
  - Dr. David Blakey, Director, Health and Safety Bureau, Health Canada
- Initial participating validation organizations
  - ECVAM
  - Health and Safety Bureau, Health Canada
  - JaCVAM
  - NICEATM-ICCVAM

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NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) Bisphenol A Review - Update

- Board of Scientific Counselors peer review of draft NTP Brief - June 11, 2008
- Final NTP-CERHR Monograph on Bisphenol A issued - September 3, 2008
  - NTP Brief on Bisphenol A
  - CERHR Expert Panel Report on Bisphenol A
  - Public comments and peer review report on bisphenol A
  - *Some concern* for effects on brain, behavior, and prostate gland, and *minimal concern* for effects on the mammary gland and an earlier age for puberty in females in fetuses, infants, and children at current human exposures

NTP Bisphenol A Update - continued

- NTP presentation to FDA Science Board Subcommittee - September 16, 2008
- FDA response to Science Board' recommendations - February 24, 2009
  - Apply BMD methodology instead of NOAELs with safety factors
  - Characterize uncertainties in studies used for risk assessment
  - Extend infant exposure assessment and collect additional information on bisphenol A content in formula and contributions from baby bottles
  - Re-evaluate studies deemed "adequate" by NTP
  - Design pharmacokinetic studies in adult, neonatal, and fetal rats and non-human primates
  - Develop protocols for perinatal subchronic and chronic studies in rodents, a neurodevelopmental study in rats, and growth and cognitive and pubertal development in rhesus monkeys
  - Evaluate bisphenol A in medical devices - dental sealants, containers for drugs and biologics, hemodialysis, and cardiopulmonary bypass circuits

NTP Bisphenol A Update - continued

- NTP and NIEHS/Division of Extramural Research and Training issued Request for Information: Ongoing Research and Research Needs for Biological Effects of Exposure to Bisphenol A - October 20, 2008
- Consideration of studies to support PBPK models in rodents and non human primates, and perinatal exposure studies for long-term developmental follow-up
  - Discussed at TSSRC meetings, November 18, 2008 and May 20, 2009
  - Effort to involve academic community
- Editorial - Bisphenol A: Where to Now? EHP [Vol. 117, page A96, March 2009]

NTP Bisphenol A Update - continued

- NIEHS American Recovery and Reinvestment Act: Grand Opportunity
  - Bisphenol A: Research to Impact Human Health
  - 2-year, $5 M grants program, 41 applications received
  - Develop new data in strategic areas to address existing experimental limitations using developmental exposure to low doses; animal or human studies
    - Obesity, diabetes, metabolic syndrome
    - Reproductive disorders, age at puberty
    - Development of prostate, mammary, or uterine cancer
    - Immune dysfunction
    - Cardiovascular disease
    - Trans generational effects
    - PBPK models

NTP Bisphenol A Update - continued

- NIH/FDA BPA Task Force - survey of epidemiology studies
  - Review of epidemiology studies with spot urine or blood collections
    - Primarily adult exposures looking at cardiovascular disease or diabetes
      - Are urinary bisphenol A concentrations associated with diabetes, myocardial infarction, stroke, or cancer?
        - Atherosclerosis Risk in Communities Study
        - Women's Health Initiative
        - Multi-ethnic Study of Atherosclerosis
    - NIEHS Children's Center longitudinal birth cohort studies (3 currently measuring bisphenol A in urine and blood along with neurodevelopment and growth)
      - Mt. Sinai
      - Columbia
      - University of California, Berkeley
  - Review of analytical methodologies - critical parameters

NTP Bisphenol A Update - continued

- Bisphenol A evaluated as part of EPA's ToxCast Phase 1
  - 467 biochemical and cell-based assays
  - 9 different technologies
  - Bisphenol A active in ~100 endpoints
- Manuscript by Judson *et al.* in preparation
- Stay tuned

NTP Bisphenol A Update - continued

- Other Activities
  - Senator Schumer announces BPA-Free Kids Act - March 30, 2009
    - Prohibits sale of bisphenol A containing food and beverage containers for infants and children
    - Directs NIEHS to begin a 5-year research initiative to understand health effects
  - Minnesota bans bisphenol A in sippy cups and baby bottles - May 11, 2009
  - Chicago bans sale of baby bottles and sippy cups containing bisphenol A - May 14, 2009
  - 24 states have legislation pending
  - FDA Commissioner Hamburg announces reassessment - June 3, 2009
  - Cal EPA hearing to list bisphenol A under Prop. 65 - July 15, 2009